



# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/060,759	01/30/2002	Adam Lerner	701586/50174-DIV	8480
50607 7590 03/25/2009 RONALD I. EISENSTEIN 100 SUMMER STREET NIXON PEABODY LLP BOSTON, MA 02110				
EXAMINER				
ANDERSON, JAMES D				
ART UNIT		PAPER NUMBER		
1614				
MAIL DATE		DELIVERY MODE		
03/25/2009		PAPER		

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/060,759

**Applicant(s)**

LERNER, ADAM

**Examiner**

JAMES D. ANDERSON

**Art Unit**

1614

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 16 January 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-7, 15 and 16 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-7, 15 and 16 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-8508)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Formal Matters***

Applicants' response and amendments to the claims, filed 1/16/2009, are acknowledged and entered. Claims 1-7, 15, and 16 are pending and under examination.

The indication of allowable subject matter (claim 15) in the previous Office Action is withdrawn in light of the new rejections set forth below.

### ***Declaration under Rule 1.132***

The Examiner acknowledges receipt of the Rule 1.132 Declaration of Adam Lerner ("3<sup>rd</sup> Lerner Declaration") and has carefully considered the information provided therein.

### ***Claim Rejections - 35 USC § 112 – 1<sup>st</sup> Paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 and 16 are again rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1<sup>st</sup> "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are drawn to a method comprising administering to a subject a therapeutically effective amount of an inhibitor that specifically inhibits Type 4 cyclic adenosine monophosphate phosphodiesterases.

*Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in

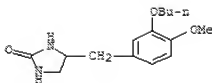
possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claims indicates that these claims are drawn to a generic genus, *i.e.*, a method of treating CLL with an inhibitor of PDE4.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

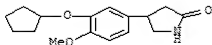
A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(i), the court states, "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

Accordingly, the courts have repeatedly held that description of a genus defined only by functional activity does not provide adequate written description of the genus unless accompanied by disclosure of structural features common to members of the genus and/or by disclosure of a representative number of species falling within the scope of the genus. The Examiner respectfully submits that Applicant fails to disclose structural features common to members of the claimed genus and/or a representative number of species falling within the scope of the claimed genus.

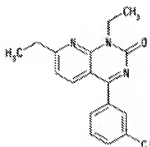
There are **two** species of the claimed genus disclosed that are within the scope of the claimed genus, *i.e.* rolipram and XX5 (page 5, lines 2-9). The disclosure of a single disclosed species (or two species) may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claims encompass numerous species that are not further described. There do not appear to be any structural features common to the claimed genus of inhibitors that specifically inhibit type 4 PDE. Structures of some type 4 PDE inhibitors are shown below.



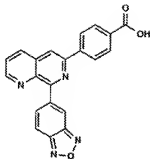
**XX5, RO-1724 (disclosed by Applicants)**



**Rolipram (disclosed by Applicants)**



**YM976 (Aoki et al.)**



**NVP-ABE171 (Trifileff et al.)**

Clearly, Applicants recitation of rolipram and XX5 fail to disclose structural features common to members of the genus and are not a representative number of species falling within the disclosed genus.

Applicants explicitly define the term “an inhibitor that specifically inhibits Type 4 cyclic adenosine monophosphate phosphodiesterase” as a compound that inhibits Type 4 but not Type 1 or 3 phosphodiesterases (page 4, lines 6-8). However, Applicants additionally state that “background level inhibition of Type 1 or 3 phosphodiesterases is permitted within the definition” (*id.* at lines 8-9). While no definition of “background level inhibition” is provided by Applicants, Applicants do state that where an inhibitor inhibits Type 4 as well as Type 1 and/or 3, but inhibits Type 4 to a greater extent, the phrase “*preferentially* inhibits Type 4 phosphodiesterases” is used herein (as distinct from “Type 4 specific”). To what extent the Type 4 inhibition has to be “greater” than Type 1 and/or 3 inhibition to constitute preferential versus specific inhibition is not disclosed in the specification (*i.e.*, Applicants have not described what constitutes background level inhibition versus what constitutes preferential inhibition). For example, would a compound that inhibits Type 4 PDE with an  $IC_{50}$  of 10 nM and Type 1 PDE with an  $IC_{50}$  of 1  $\mu$ M be considered a “preferential” inhibitor of Type 4 PDE or a “specific” inhibitor of Type 4 PDE? The compound clearly *inhibits* Type 1 PDE and thus does not appear to fall within Applicant’s definition of not inhibiting Type 1 or 3 PDE. Alternatively, Applicant could consider the inhibition of Type 1 PDE to be “background level inhibition”.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus, which is a method of treating CLL with a generic genus of inhibitor compounds, *i.e.*, specific inhibitors of Type 4 PDE

purported to have activity in treating chronic myelogenous leukemia. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Applicant's arguments have been considered but are not persuasive. Applicant argues that the 3<sup>rd</sup> Lerner Declaration clearly explains that based on the level of skill in the art and the widely available knowledge about PDEs and their inhibitors in general and PDE4 specific inhibitors particularly, and in view of the specification, a skilled artisan "knows that the class of compounds useful according to the invention is specific PDE4 inhibitors". The Examiner does not dispute that the skilled artisan knows what is presently claimed. Rather, the Examiner maintains that disclosure of two PDE4 inhibitors (*i.e.*, rolipram and XX5) and their use in treating CLL does not put Applicant in possession of treatment methods using the broad genus of PDE4 inhibitors presently being claimed, especially in view of Applicant's definition of "an inhibitor that specifically inhibits Type 4 cyclic adenosine monophosphate phosphodiesterase", which allows for "background level inhibition" of Type 1 or Type 3 phosphodiesterases.

The Declarations of Dr. Lerner filed 4/25/2008 and 1/16/2009 provide Exhibits in the form of prior art alleged to disclose the genus of specific PDE4 inhibitors encompassed by the claims. Dr. Lerner states that a number of other *specific* PDE4 inhibitors were well known to the skilled artisan, such as RP73401, LAS31025, SB207499, CDP840, CP80633, CP77059, BRL61063, denbufylline, and MNS949. However, the fact that other PDE4 inhibitors might have been known does not obviate the present rejection, because the instant claims require inhibitors that *specifically* inhibit Type 4 cyclic adenosine monophosphate phosphodiesterases. By Applicant's definition, these inhibitors inhibit Type 4 but not Type 1 or 3 phosphodiesterases. Applicant also states that background level inhibition of Type 1 or 3 phosphodiesterases is permitted within the definition, but where the inhibitor inhibits Type 4 as well as Type 1 and/or 3, but inhibits Type 4 to a greater extent (the amounts being subject to quantitative determination by assays described herein), the phrase "preferentially inhibits Type 4 phosphodiesterases" is used herein (as distinct from "Type 4 specific"). Thus, it appears that the

claimed inhibitors that *specifically* inhibit Type 4 cyclic adenosine monophosphate phosphodiesterases cannot inhibit Type 1 or Type 3 cyclic adenosine monophosphate phosphodiesterases to a greater extent than Type 4 (Applicant does not define what “background level inhibition” means). No evidence has been submitted that the “PDE4 inhibitors” known in the art do not inhibit Type 1 or Type 3 PDEs at all or only have background level inhibition of such enzymes as required by Applicant's definition of compounds that “*specifically* inhibit Type 4 cyclic adenosine monophosphate phosphodiesterases” as opposed to compounds that *preferentially* inhibit Type 4 phosphodiesterases. Thus, while PDE4 inhibitors appear to be known in the art (*i.e.*, inhibitors that inhibit PDE4), “specific” PDE4 inhibitors as defined by Applicant (*i.e.*, those inhibitors that inhibit PDE4 but not PDE1 or PDE3) are not well known in the art as asserted by Applicant. Even those PDE4 inhibitors listed in the cited Teixeira *et al.* reference are only referred to as “PDE4 inhibitors”. There is no teaching that the listed inhibitors are “specific” to PDE4 as defined by Applicant.

The Examiner has reviewed the cited exhibits but has not found any factual evidence that compounds disclosed therein inhibit Type 4 PDE with only “background level inhibition of Type 1 or 3 phosphodiesterases”. For example, Exhibit B of the 2nd Lerner Declaration filed 4/25/2008 (Teixeira *et al.*) discusses “Phosphodiesterase (PDE) 4 Inhibitors”, but does not define what is meant by “PDE4 inhibitor”. From the disclosure of Teixeira *et al.*, all that can be gathered is that the compounds disclosed in Table 2 inhibit Type 4 PDE. Whether these compounds inhibit Type 4 but not Type 1 or Type 3 PDE as defined by Applicants cannot be ascertained.

Applicant argues that the pending claims are not directed to a genus of PDE4 inhibitors but rather to a method for treating CLL using PDE4 specific inhibitors. The Examiner is aware that the claims are not directed to the genus of PDE4 specific inhibitors *per se*. However, this fact does not obviate the requirement under 35 U.S.C. 112, 1<sup>st</sup> paragraph for Applicant to provide a written description of the genus of compounds intended to be used in the claimed methods.

Accordingly, in view of Applicant's disclosure of only two specific compounds (*i.e.*, rolipram and XX5) and further in view of Applicant's definition of “an inhibitor that specifically inhibits Type 4 cyclic adenosine monophosphate phosphodiesterase” as a compound that inhibits Type 4 but not Type 1 or 3 phosphodiesterases (page 4, lines 6-8), the instant specification fails



to provide adequate written description of the class of compounds useful in the methods of the present claims.

The rejection of claims 1-7 and 16 under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for treating CLL with rolipram or XX5, does not reasonably provide enablement for treating CLL in a patient with other inhibitors of Type 4 adenosine monophosphate phosphodiesterase is withdrawn in light of Applicant's arguments and newly discovered art.

***Claim Rejections - 35 USC § 103 – New Grounds of Rejection***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Fowler *et al.*** (USP No. 6,294,561; Issued Sep. 25, 2001; Filed Nov. 14, 2000) (newly cited) in view of **van Kooten *et al.*** (Leukemia and Lymphoma, 1993, vol. 12, pages 27-33) (newly cited).

Fowler *et al.* disclose compounds that are potent and selective inhibitors of PDE4 for use in the treatment of diseases involving elevated levels of cytokines (Abstract). The inventors disclose that elevated levels of cAMP in human myeloid and lymphoid lineage cells are associated with the suppression of cell activation (col. 2, lines 30-32) and that PDE4 is a major contributor to cAMP degradation (*id.* at lines 33-35). Further, PDE4 inhibitors such as rolipram have been shown to inhibit production of TNF $\alpha$  and partially inhibit IL-1 $\beta$  release by monocytes (*id.* at lines 44-46). Inflammatory cell activation and excessive or unregulated cytokine (*e.g.*, TNF $\alpha$  and IL-1 $\beta$ ) production are implicated in proliferative lymphocyte diseases such as leukemia (col. 2, line 60 to col. 3, line 11). Accordingly, Fowler *et al.* developed compounds of formula (II) (col. 5, lines 5-65) as selective inhibitors of PDE4 for the treatment of diseases associated with excessive or unregulated production of cytokines, such as TNF or diseases that

are associated with elevated cAMP levels or PDE4 function in a particular target tissue (col. 4, lines 55-64; col. 12, lines 63-65; col. 13, lines 15-28).

Fowler *et al.* suggest that the compounds of their invention are useful in treating proliferative lymphocytic diseases such as leukemia, specifically chronic lymphocytic leukemia as recited in the instant claims (col. 14, lines 3-5; claim 28).

Formulations of the PDE4 inhibitors disclosed in Fowler *et al.* can be administered in a standard manner for the treatment of the indicated disease, such as orally, parenterally, transmucosally, topically, transdermally, rectally, or via inhalation as recited in claims 2-4 (col. 15, lines 44-53).

van Kooten *et al.* is cited as evidence that cytokines such as TNF $\alpha$  are involved in the regulation of B-CLL proliferation and that increased levels of cAMP dose-dependently inhibit the TNF $\alpha$ -induced proliferation of B-CLL (Abstract). In this regard, an inhibitor of cAMP breakdown (IBMX) was demonstrated to result in a dose-dependent inhibition of CLL proliferation (page 29, right column; Figure 3A). The phosphodiesterase inhibitor, pentoxifylline, was also shown to inhibit the proliferation of B-CLL cells (Figure 6). In summary, the authors suggest that addition of drugs leading to enhanced levels of intracellular cAMP can be used to inhibit the growth of B-CLL cells.

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the specific PDE4 inhibitors disclosed in Fowler *et al.* to treat patients having chronic lymphocytic leukemia. The skilled artisan would have been motivated to do so because Fowler *et al.* explicitly suggest the treatment of chronic lymphocytic leukemia and van Kooten *et al.* demonstrate that compounds that inhibit TNF $\alpha$  and/or increase intracellular cAMP levels in CLL cells inhibit proliferation of such cells. As such, because the specific PDE4 inhibitors disclosed in Fowler *et al.* are suggested to be useful in the treatment of diseases associated with excessive or unregulated production of cytokines, such as TNF, or diseases that are associated with elevated cAMP levels or PDE4 function in a particular target tissue, the skilled artisan would have been imbued with at least a reasonable expectation that administration of a compound of Fowler *et al.* would inhibit PDE4 in CLL cells which would

result in increased intracellular levels of cAMP thus resulting in inhibition of CLL cell proliferation as demonstrated in van Kooten *et al.*

With regard to claims 5-6, while Fowler *et al.* do not explicitly disclose the treatment of naive CLL patient or immunocompromised CLL patients, one skilled in the art at the time the invention was filed would have been imbued with at least a reasonable expectation that inhibition of PDE4 would result in increased intracellular levels of cAMP as suggested by the cited prior art in such patients. As such, administration of a PDE4 inhibitor disclosed in Fowler *et al.* to such patients would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was filed.

Claims 7 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Fowler *et al.*** (USP No. 6,294,561; Issued Sep. 25, 2001; Filed Nov. 14, 2000) (newly cited) in view of **van Kooten *et al.*** (Leukemia and Lymphoma, 1993, vol. 12, pages 27-33) (newly cited) as applied to claims 1-6 above, and further in view of **Mentz *et al.*** (Blood, 1996, vol. 88, no. 6, lines 2172-2182) (newly cited).

Fowler *et al.* and van Kooten *et al.* disclose as applied *supra* and are herein applied for the same teachings in their entirety. Claims 7 and 16 differ from the primary and secondary references in that the references do not disclose administration of a PDE4 inhibitor to a patient unresponsive to chemotherapy with alkylating agents or combining a PDE4 inhibitor with a cytotoxic drug to augment apoptosis in CLL cells.

However, Mentz *et al.* teach that the phosphodiesterase inhibitor, theophylline, induces intracellular accumulation of cAMP in malignant B cells from CLL patients and induces apoptosis in such cells. A synergistic effect was observed when theophylline was administered with the alkylating agent chlorambucil (Abstract; Table 1; Figure 2; Figure 4). Rapid and marked responses of this combination were observed in CLL patients with progressive or recurrent aggressive CLL after standard chemotherapy (page 2180, right column).

As such, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have administered a combination of a PDE4 inhibitor disclosed in Fowler *et al.* and the alkylating agent chlorambucil to CLL patients unresponsive to chemotherapy with alkylating agents. The skilled artisan would have been imbued with at least

as reasonable expectation that such a combination would be an effective treatment for these patients given the demonstrated efficacy of the PDE inhibitor theophylline when used in combination with chlorambucil as demonstrated in Mentz *et al.* It is clear that the biological effect of theophylline (*i.e.*, increased cAMP concentration) is the same as that of the PDE4 inhibitors taught in Fowler *et al.* and suggested to be useful in the treatment of CLL as taught in van Kooten *et al.*

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Fowler *et al.*** (USP No. 6,294,561; Issued Sep. 25, 2001; Filed Nov. 14, 2000) (newly cited) in view of **van Kooten *et al.*** (Leukemia and Lymphoma, 1993, vol. 12, pages 27-33) (newly cited) and **Jiang *et al.*** (Proc. Natl. Acad. Sci. USA, 1996, vol. 93, pages 11236-11241).

Fowler *et al.* and van Kooten *et al.* disclose as applied *supra* and are herein applied for the same teachings in their entirety. Claim 15 differs from Fowler *et al.* and van Kooten *et al.* in that the references do not teach the claimed PDE4 inhibitor, 4-(3-butoxy-4-methoxybenzyl)-2-imidazolidinone.

However, Jiang *et al.* teach that rolipram and RO-20-1724 are inhibitors of PDE4 that induce apoptosis of the human lymphoblastoid B-cell line, RPMI-8392 (page 11238, paragraph bridging left and right columns). The authors suggest that PDEs, particularly PDE1B1, may be useful targets for inducing the death of leukemic cells (Abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the PDE4 inhibitors rolipram or RO-20-1724 to treat CLL according to the methods suggested and motivated by Fowler *et al.*, van Kooten *et al.*, and Jiang *et al.* As discussed *supra*, Fowler *et al.* teach and suggest the treatment of CLL using specific inhibitors of PDE4 so as to decrease TNF $\alpha$  levels and/or increase the intracellular levels of cAMP. Van Kooten *et al.* teach that cytokines such as TNF $\alpha$  are involved in the regulation of B-CLL proliferation and that increased levels of cAMP dose-dependently inhibit the TNF $\alpha$ -induced proliferation of B-CLL. Jiang *et al.* teach that the inhibitors of PDE4, rolipram and RO-20-1724, induce apoptosis of leukemia cells. As such, the skilled artisan would have been imbued with at least a reasonable expectation that RO-20-1724, having the same biological

activity as the PDE4 inhibitors disclosed in Fowler *et al.*, would thus also be useful to treat the same conditions and diseases suggested by Fowler *et al.*, including CLL as also suggested and motivated by the teachings of van Kooten *et al.*

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/  
Examiner, Art Unit 1614

/Ardin Marschel/  
Supervisory Patent Examiner, Art Unit 1614